Amendments to the Specifications:

Please replace the paragraph starting at page 4, line 21 of the specification with the following paragraph:

In Alzheimer's disease, for example, the 39-43-residue Aβ peptide aggregates into amyloid fibrils by the intermolecular association of five-residue peptide segments comprising the sequence KLVFF (SEQ ID NO: 1) ~~(SEQ. ID. NO.1)~~ (corresponding to residues 16-20 of the Aβ peptide) (Tjernberg et al., 1997; Tjernberg et al., 1996). The peptide segments form β-strands which associate to form an extended antiparallel β-sheet by means of hydrophobic interactions between their side chains and hydrogen bonds between their backbone amide groups. This fibrogenic association can be inhibited by short peptides which also contain the KLVFF sequence (SEQ ID NO: 1) ~~(SEQ. ID. NO.1)~~ or a homologous sequence, such as Ac-QKLVFF-NH2 (Tjernberg et al., 1996), GQKLVFFAEDVGG-[NH(CH2)5CO]-K6 (Ghanta et al., 1996), and KKLVFFA (SEQ ID NO: 4) (Tjernberg et al., 1997). These peptides form β-strands which compete for association with the homologous sequence in the Aβ peptide and thereby hinder its aggregation. The first of these peptides has a limited solubility in aqueous solutions because it too can aggregate into extended β-sheets. The latter two peptides, on the other hand, are more water-soluble because they contain more polar groups, but are consequently too hydrophilic to penetrate cell membranes and the blood-brain barrier. Peptides can be made more soluble without compromising their hydrophobicity by including proline residues rather than polar residues. For example, the peptides RDLPFFPVPID, LPFFPVD, and LPFFD have a similar degree of hydrophobicity as the Aβ peptide, but are highly soluble in aqueous solutions because the proline residues sterically prevent them from forming β-strands which aggregate into extended β-sheets (Soto et al., 1996; Soto et al., 1998). However, these peptides are less potent inhibitors of Aβ-peptide aggregation because the β-strand conformation is actually required for making strong and specific interactions with the β-strands formed by the Aβ peptide, in order to inhibit their

aggregation. In short, nobody has discovered how to prevent the peptides from aggregating in aqueous buffers without compromising their hydrophobicity, which is required for effective penetration of cell membranes and the blood-brain barrier, or their potency as inhibitors of protein and peptide aggregation.

Please replace the paragraph starting at page 5, line 27 of the specification with the following paragraph:

In addition to this problem of solubility versus hydrophobicity and potency, all the peptides mentioned above are extremely susceptible to degradation by proteolytic enzymes because they consist entirely of Nα-unsubstituted ~~α-L-amino-acid~~ α-L-amino acid residues, and are therefore unsuitable for use as therapeutic agents. This particular problem has been addressed by designing peptides that consist only of ~~α-D-amino-acid~~ α-D-amino acid residues, which are not recognised by proteolytic enzymes (Miller et al., 1995). For example, all-D-[RDLPFFPVPID] (Soto et al., 1996) and all-D-[LFLRR] (Tjernberg et al., 1997) are highly resistant to enzyme-catalysed proteolysis as expected, but these peptides still face the problem of conflict between solubility in aqueous buffers, ability to penetrate cell membranes and the blood-brain barrier, and ability to inhibit the aggregation of other proteins and peptides into insoluble β-fibres.

Please replace the paragraph starting at page 6, line 8 of the specification with the following paragraph:

It is known that peptides containing Nα-substituted or ~~α-D-amino-acid~~ α-D-amino acid residues are much less susceptible to enzyme-catalysed proteolysis than peptides which consist only of Nα-unsubstituted ~~α-L-amino-acid~~ α-L-amino acid residues because neither Nα-substituted nor α-D-amino acid ~~α-D amino-acid~~ residues are not recognised by proteolytic enzymes (Miller et al., 1995). Peptides containing Nα-substituted ~~amino-acid~~ amino acid residues are also much less likely

to aggregate into insoluble β-fibres in aqueous solutions because the Nα atoms of these residues are not available for hydrogen bonding and, moreover, because their Nα substituents sterically disallow the association of β-strands. A peptide has been designed containing Nα-methyl amino acid ~~amino-acid~~ residues which folds into a three-stranded β-sheet, but which does not aggregate into extended β-sheets because the Nα-methyl groups of these residues sterically prevent it from doing so (Doig, 1997). In this peptide, the two peripheral β-strands each contain a sequence of two Nα-methyl alanine residues separated by a single Nα-unsubstituted alanine residue, so that all four Nα-methyl groups lie along the outer edges of these two β-strands, while the inner edges remain free to associate with the central β-strand, thereby forming the three-stranded β-sheet. However, it has not previously been reported that such a peptide is, in isolation, able to associate with β-strands formed by other protein or peptide molecules and thereby inhibit their aggregation into extended β-sheets and insoluble β-fibres. Moreover, it has not previously been reported that a peptide comprising Nα-substituted and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues is able to associate specifically with β-strands formed by other protein or peptide molecules and thereby inhibit their aggregation into extended β-sheets and insoluble β-fibres.

Please replace the paragraph starting at page 7, line 7 of the specification with the following paragraph:

In accordance with a first aspect of the present invention, therefore, there is provided a chemical compound or composition comprising a peptide, which peptide comprises a β-strand-forming section of peptide which forms a β-strand and associates as such with a target β-strand formed by a separate peptide-containing molecule, or comprising a component which mimics the structure and action of said β-strand-forming section of peptide, wherein the β-strand-forming section of peptide comprises a sequence of at least four consecutive ~~α-D-amino-~~

~~acid~~ α-D-amino acid residues, all of which sterically permit the β-strand-forming section of peptide to form a β-strand, and at least one of which is an Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residue, and any two successive Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues are separated by an odd number of consecutive Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues.

Please replace the paragraph starting at page 7, line 24 of the specification with the following paragraph:

A β-strand is a section of peptide whose backbone takes on the form of an extended ribbon; the side chains of consecutive residues in a β-strand protrude from alternate sides of the plane of the ribbon, while the NH and CO components of the backbone peptide groups lie along the two edges of the ribbon. β-strands are regular structures that are only formed by sections of peptide which consist solely of ~~α-L-amino-acid~~ α-L-amino acid residues or solely of ~~α-D-amino-acid~~ α-D-amino acid residues; the phi and psi angles of each amino-acid residue in a β-strand are close to -120° and +120° respectively. β-strands are not stable in isolation, and exist only when two or more of them are associated to form a parallel or antiparallel β-sheet. The individual β-strands in a β-sheet are held together side by side and edge to edge in either parallel or antiparallel orientation by hydrogen bonds between the NH and CO components of their backbone peptide groups, as well as by additional non-covalent interactions between their side chains. A β-strand has two edges, each of which can support the association of another β-strand in this way. A β-sheet can therefore be extended indefinitely by the progressive addition of more β-strands to the free edges of its two peripheral β-strands; this eventually results in the formation of insoluble β-fibres.

Please replace the paragraph starting at page 9, line 21 of the specification with the following paragraph:

The invention moreover relates to chemical compounds and compositions comprising components which mimic the structure and action of a β-strand and are thus peptide mimics. A "peptide mimic" refers to a peptide wherein one or more of the backbone peptide groups or side-chain groups have been replaced by another chemical group of similar stereochemistry and ability to form favourable non-covalent interactions with the target β-strand. For example, each backbone peptide group (CONH) could be replaced by one of the following groups: CSNH (thioamide); COO (ester); CSO/~~,~~ COS~~, CSS~~ (thioester); CSS (dithioester); COCH2 (ketone); CSCH2 (thioketone); SO2NH (sulphonamide); SOCH2 (sulphoxide); SO2CH2 (sulphone); SO2O (sulphonate). Each N-substituted backbone peptide group could be replaced by an N- or C-substituted form of one of the following groups: CSNH (thioamide); COCH2 (ketone); CSCH2 (thioketone); SO2NH (sulphonamide); SOCH2 (sulphoxide); SO2CH2 (sulphone). And each side chain could be replaced by another group having a similar stereochemistry or arrangement of polar and non-polar atoms, as long as any particular features which are essential for association with the target β-strand are preserved.

Please replace the paragraph starting at page 10, line 7 of the specification with the following paragraph:

The use of Nα-substituted ~~α-D-amino-acids~~ α-D-amino acid is highly advantageous. All ~~α-D-amino-acids~~ α-D-amino acid are resistant to protease attack, and Nα-substituted ~~α-D-amino-acids~~ α-D-amino acid are also suitable for sterically hindering β-sheet formation. Resistance to protease attack is a preferred property in the context of the present invention

Please replace the paragraph starting at page 14, line 7 of the specification with the following paragraph:

Figures 3 and 4 show how Peptide X (~~SEQ. ID. NO. 2~~ SEQ ID NO: 2) forms a β-strand (X) and associates as such with one edge of a target β-strand (Y) formed by a segment of the Aβ peptide or some other

peptide-based molecule in either orientation to form a parallel (Fig. 3) or antiparallel (Fig. 4) two-stranded β-sheet complex, thereby sterically hindering the association of other β-strands with that edge of the target β-strand. In each of these two figures: the target β-strand comprises a sequence of eight consecutive ~~α-L-amino-acid~~ α-L-amino acid residues, the Cα atoms of which have not been labelled; the Cα atoms of the six ~~α-D-amino-acid~~ α-D-amino acid residues of Peptide X (~~SEQ. ID. NO. 2~~ SEQ ID NO: 2) are numbered from the N-terminus, while the Cα atom of its N-terminal acetyl group is indicated by a letter A; only the non-hydrogen backbone atoms of these two β-strands - including the Nα-methyl carbon atoms of the two ~~Nα-methyl-α-D-amino-acid~~ Nα-methyl-α-D-amino acid residues (residues 2 and 4) of Peptide X (~~SEQ. ID. NO. 2~~ SEQ ID NO: 2) - are shown, and are represented by symbols defined by the atom key below the figures; hydrogen bonds between backbone amide groups of the two β-strands are indicated by dashed lines.

Please replace the paragraph starting at page 14, line 28 of the specification with the following paragraph:

Figure 5 is a graph showing the prevention of Alzheimer's Aβ peptide aggregation into β-sheet structures after administration of Peptide X (~~SEQ. ID. NO. 2~~ SEQ ID NO: 2). A 50% reduction in Alzheimer's Aβ peptide aggregation is seen at a Peptide X (~~SEQ. ID. NO. 2~~ SEQ ID NO: 2) concentration of 100mM.

Please replace the paragraph starting at page 15, line 4 of the specification with the following paragraph:

Figure 7 is an electron micrograph showing Alzheimer's Aβ peptides incubated at a concentration of 500mM in the presence of Peptide X (~~SEQ. ID. NO. 2~~ SEQ ID NO: 2); electron microscope examination shows a substantial elimination of aggregation.

Please replace the paragraph starting at page 15, line 19 of the specification with the following paragraph:

The peptide according to the present invention comprises a section which is able to form a β-strand, because it consists solely of ~~α-D-amino-acid~~ α-D-amino acid residues which sterically permit it to do so. On top of this, the steric constraints imposed by the Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residue(s) and by any β-branched ~~α-D-amino-acid~~ α-D-amino acid residue(s) in the β-strand-forming section of peptide may serve to encourage β-strand formation. When the β-strand-forming section of peptide forms a β-strand, the Nα-substituents of its Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues are positioned, by design, so as to lie along only one of its two edges. The Nα-substituted residues are spaced such that they are separated by odd numbers of residues, since the repeating unit of a β-strand is two residues. For example, between any two successive Nα-substituted residues there may lie 1 or 3 Nα-unsubstituted residues.

Please replace the paragraph starting at page 17, line 5 of the specification with the following paragraph:

As used herein, a "peptide" is a polymer in which the monomers are ~~amino-acids~~ amino acids and are joined together by peptide bonds. The length of a β-strand-forming section of peptide according to the invention will be determined empirically, as described in detail below; however, the β-strand-forming section of peptide is at least 4 ~~amino-acid~~ amino acid residues in length, and preferably between about 4 and about 50 ~~amino-acids~~ amino acid residues in length; advantageously between about 4 and about 16 ~~amino-acids~~ amino acid residues in length, and most preferably between about 5 and about 10 ~~amino-acids~~ amino acid residues. Preferably, the β-strand-forming section of peptide is no longer than the target β-strand, and at least as long as the aggregation-causing section of the target β-strand.

Please replace the paragraph starting at page 17, line 19 of the specification with the following paragraph:

The amino-acid monomers of which the β-strand-forming section of peptide is constructed are ~~α-D-amino-acids~~ α-D-amino acids, meaning that they are of the D-enantiomeric from as opposed to the L-enantiomeric form. ~~L-amino-acids~~ D-amino acids, which commonly occur in nature, are susceptible to digestion by protease enzymes if unprotected. Nα-substituted ~~α-D-amino-acids~~ α-D-amino acids are ~~α-D-amino-acids~~ α-D-amino acids which carry a substituent, which is not hydrogen, on the α-N atom, whilst Nα-unsubstituted ~~α-D-amino-acids~~ α-D-amino acids have no substituent at this position. Preferred substituents useful for practising the subject invention are set forth below. In general, however, the substituents must be large enough to sterically hinder the association of β-strands, and preferably large enough to hinder or prevent proteolytic degradation of the peptide but they must not hinder the β-strand forming section of peptide from forming a β-strand.

Please replace the paragraph starting at page 19, line 3 of the specification with the following paragraph:

In order that the β-strand-forming section of peptide is able to form a β-strand, it must consist solely of ~~α-D-amino-acid~~ α-D-amino acid residues which sterically permit the β-strand-forming section of peptide to form a β-strand. Proline, for example, cannot be included in the β-strand-forming section of peptide except at its very ends because its side chain is joined back onto its backbone nitrogen atom, and therefore it is unable to adopt the phi angle required to form a β-strand.

Please replace the paragraph starting at page 20, line 9 of the specification with the following paragraph:

The target β-strand, the aggregation-causing segment of that target β-strand and therefore the optimal length for the β-strand-forming section of a peptide according to the present invention, may be determined empirically. For example, the target β-strand may be identified as a section of peptide in a protein or peptide molecule which forms a β-strand and undesirably aggregates or associates as such with other β-strands to form a β-sheet or β-fibre. The aggregation-causing segment of this target β-strand can then be identified as a section of at least four residues mostly having hydrophobic and/or amide-containing side chains, or can be determined experimentally by investigating the association properties of short segments of the target β-strand or of single-residue mutants of the target β-strand. For example, a section of the 39-43-residue Alzheimer's Aβ peptide forms a β-strand and undesirably aggregates as such into insoluble β-fibres. This β-strand is therefore identified as the target β-strand, and its aggregation-causing segment has been identified as having the sequence KLVFF (~~SEQ. ID. NO. 1~~ SEQ ID NO: 1)by investigating the association properties of short segments of the Aβ peptide and single-residue mutants thereof: truncation of this segment at either end, or substitution of any of its residues by alanine dramatically reduced the tendency of the Aβ peptide to aggregate into insoluble β-fibres (Tjernberg et al., 1997; Tjernberg et al., 1996).

Please replace the paragraph starting at page 21, line 14 of the specification with the following paragraph:

The β-strand-forming section of peptide preferably contains the same number of residues as the aggregation-causing segment of the target β-strand, and advantageously comprises a sequence of alternating ~~Nα-methyl-α-D-amino-acids~~ Nα-methyl-α-D-amino acids and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues. The side chains of the residues in the β-strand-forming section of peptide are complementary

to those of the aggregation-causing segment of the target β-strand in the same order, by which is meant the side chain of the first residue of the β-strand-forming section of peptide is chosen to form a favourable non-covalent interaction with the side chain of the first residue of the aggregation-causing segment of the target β-strand, and so on. For example: if the first residue of the aggregation-causing segment of the target β-strand has an amide-containing side chain, then the first residue of the β-strand-forming section of peptide should also have an amide-containing side chain; if the first residue of the aggregation-causing segment of the target β-strand has a hydrophobic side chain, then the first residue of the β-strand-forming section of peptide should also have a hydrophobic side chain; if the first residue of the aggregation-causing segment of the target β-strand has a hydroxyl-containing side chain, then the first residue of the β-strand-forming section of peptide should also have a hydroxyl-containing side chain; if the first residue of the aggregation-causing segment of the target β-strand has a basic side chain, then the first residue of the β-strand-forming section of peptide should have an acidic side chain; and if the first residue of the aggregation-causing segment of the target β-strand has an acidic side chain, then the first residue of the β-strand-forming section of peptide should have a basic side chain. This selection procedure is continued for all the remaining side chains in the β-strand-forming section of peptide.

Please replace the paragraph starting at page 22, line 13 of the specification with the following paragraph:

In general, a suitable sequence of side chains in the β-strand-forming section of peptide can also be taken directly from the section of the β-strand which undesirably associates with the aggregation-causing section of the target β-strand. For example, the Alzheimer's Aβ peptide aggregates into insoluble β-fibres by the intermolecular association of identical KLVFF <u>(SEQ ID NO: 1)</u> ~~(SEQ. ID. NO. 1)~~

aggregation-causing segments of peptide as β-strands in the antiparallel orientation, and in the resulting antiparallel β-sheet complex, the four hydrophobic side chains of each β-strand form hydrophobic interactions with those of the associated β-strand, while the basic lysine side chain of each β-strand presumably forms an electrostatic interaction with one of the two acidic side chains that follow the KLVFF sequence (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ in the associated β-strand (Tjernberg et al., 1997). Since the β-strand-forming section of peptide is designed to associate as a β-strand with the KLVFF sequence (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ in the parallel orientation, the sequence of its side chains is preferably designed to be homologous or identical to the KLVFF sequence (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ in reverse order, i.e. FFVLK (SEQ ID NO: 3 ~~SEQ. ID. NO. 3~~). Other compounds or compositions corresponding to the present invention may be designed to associate specifically with other target β-strands by a similar method.

Please replace the paragraph starting at page 24, line 10 of the specification with the following paragraph:

In order that the Nα-substituents of the Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide lie along only one of the two edges of the β-strand formed by the β-strand-forming section of peptide, the Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues are interspersed by odd numbers of unsubstituted amino-acids, unless there is only one Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residue in the β-strand-forming section of peptide, because the repeating unit of a β-strand is two residues: if any two Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide were adjacent or separated by an even number of unsubstituted residues, then their Nα substituents would lie on opposite edges of the β-strand, and neither edge of the β-strand would be able to associate with a target β-strand and thereby

sterically hinder the association of other β-strands with that target β-strand.

Please replace the paragraph starting at page 24, line 27 of the specification with the following paragraph:

In theory, therefore, the Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide could be very large numbers of residues apart, or there could be only one Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residue in the β-strand-forming section of peptide. In practice, however, successive Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide should preferably be separated by no more than 3 unsubstituted residues because the steric constraints imposed by these residues actually serve to encourage the β-strand-forming section of peptide to adopt the active β-strand conformation (Manavalan and Momany, 1980).

Please replace the paragraph starting at page 25, line 4 of the specification with the following paragraph:

In the most preferable case therefore, successive Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide are separated from each other by single unsubstituted residues so that the β-strand-forming section of peptide comprises a sequence of alternating Nα-substituted and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues. This induces the entire section of peptide to adopt an active β-strand conformation.

Please replace the paragraph starting at page 26, line 24 of the specification with the following paragraph:

The β-strand-forming propensity of the β-strand-forming section of peptide may be increased further by including Nα-substituted or Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues whose side chains sterically favour the β-strand conformation. These include ~~α-D-amino-~~

~~acid~~ α-D-amino acid residues with β-branched side chains, such as α-D-threonine, α-D-valine, α-D-isoleucine, α-D-tert-leucine, α-D-β-hydroxyvaline, and their Nα-substituted derivatives. Other ~~α-D-amino-acid~~ α-D-amino acid residues which favour the β-strand conformation, for example those with aromatic side chains such as α-D-tyrosine, α-D-phenylalanine and α-D-tryptophan, and those with aliphatic hydrophobic side chains such as α-D-leucine and α-D-methionine, plus α-D-serine and α-D-glutamine, should also be included in the β-strand-forming section of peptide if and where appropriate: they must be compatible with the chemistry of solution- or solid-phase peptide synthesis, they must not sterically hinder the association of the free edge of the β-strand formed by the β-strand-forming section of peptide with the target β-strand, and they should preferably promote the β-strand formed by the β-strand-forming section of peptide to associate tightly with the target β-strand.

Please replace the paragraph starting at page 27, line 11 of the specification with the following paragraph:

As explained above, the Nα-substituted and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide should preferably promote the β-strand-forming section of peptide to form a β-strand; but they should also preferably promote this β-strand to associate as tightly as possible with the target β-strand. For this, their side chains should form strong non-covalent interactions with the neighbouring side chains of the target β-strand when the two strands are associated with each other in the parallel or antiparallel β-sheet complex. The strongest non-covalent interactions that can exist between the neighbouring side chains of associated β-strands in aqueous solutions are hydrophobic interactions between hydrophobic side chains and hydrogen bonds between amide-containing side chains. The segment of the target β-strand most responsible for its aggregation is likely to be rich in residues which have these side chains, and therefore it is this aggregation-causing segment of the target β-strand with which the β-strand-forming section of peptide can

potentially associate most tightly. For this reason, most of the Nα-substituted and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide preferably have hydrophobic or amide-containing side chains. The preferred amino-acid residues with hydrophobic side chains include α-D-valine, α-D-leucine, α-D-isoleucine, α-D-methionine, α-D-phenylalanine, α-D-tyrosine, α-D-tryptophan, and their Nα-substituted derivatives; while the preferred amino-acid residues with amide-containing side chains include α-D-asparagine, α-D-glutamine, and their Nα-substituted derivatives. The most preferred side chain of each residue in the β-strand-forming section of peptide depends on the neighbouring side chain of the associated target β-strand in the β-sheet complex, because their stereochemistries must be compatible with the formation of a favourable non-covalent interaction between them. In general, however, the most preferred hydrophobic side chain is that of leucine because it is fairly large but relatively flexible, being able to adopt any one of nine different rotamer conformations, and can easily adapt its stereochemistry to make the most favourable hydrophobic interaction with almost any neighbouring hydrophobic side chain of an associated target β-strand; the most preferred amide-containing side chain is that of glutamine because it too is relatively flexible, and is more likely to be able to make a favourable hydrogen bond with a neighbouring glutamine or asparagine side chain of an associated target β-strand. However, any hydrophobic side chain, or side chain which has a considerable hydrophobic portion, could be included in the β-strand-forming section of peptide, as could any amide-containing side chain, as long as they did not sterically hinder the β-strand-forming section of peptide from forming a β-strand, or from associating as such with a target β-strand.

Please replace the paragraph starting at page 28, line 28 of the specification with the following paragraph:

Although most of the Nα-substituted and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of

peptide should have hydrophobic or amide-containing side chains, the remainder of the Nα-substituted and Nα-unsubstituted ~~α-D-amino-acid~~ α-D-amino acid residues in the β-strand-forming section of peptide may have side chains which are neither hydrophobic nor amide-containing, but which can nevertheless form favourable non-covalent interactions with the neighbouring side chains of an associated β-strand. For example: the acidic side chains of aspartate and glutamate may form salt bridges with the basic side chains of histidine, arginine, and lysine in an associated β-strand, and conversely, the basic side chains of histidine, arginine, and lysine may form salt bridges with the acidic side chains of aspartate and glutamate in an associated β-strand; the hydroxyl-containing side chains of serine, threonine, and β-hydroxyvaline may form hydrogen bonds with the neighbouring hydroxyl-containing side chains of an associated β-strand.

Please replace the paragraph starting at page 29, line 14 of the specification with the following paragraph:

In order that the β-sheets formed by association of the β-strands do not aggregate by stacking, the β-strand-forming section of peptide also preferably includes one or more ~~α-D-amino-acid~~ α-D-amino acid residues having a side chain which extends beyond the neighbouring side chains in the β-strand formed by the β-strand-forming section of peptide. Such an extended side chain is preferably long and preferably has a polar end, so that it does not support the stacking of β-sheets. The side chains of lysine and arginine are suitable examples of such extended side chains having a polar end.

Please replace the paragraph starting at page 30, line 3 of the specification with the following paragraph:

In order that the peptides according to the invention can be traced or detected, the β-strand-forming section of peptide may include an ~~α-D-amino-acid~~ α-D-amino acid residue having a side chain which contains a radioactive or magnetically active nucleus, such as an α-D-phenylalanine, α-D-tyrosine, or α-D-thyronine residue with one or more radioactive or magnetically active iodine or other halogen atoms substituted onto the aromatic ring(s); or the β-strand-forming section of peptide may include an ~~α-D-amino-acid~~ α-D-amino acid residue having a side chain which contains a fluorescent, coloured, or other spectroscopically detectable group, including spin labels such as the 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) groups which contain unpaired electrons. A peptide containing such a spectroscopically detectable group or a radioactive or magnetically active nucleus may be used as a traceable probe to indicate the presence and location of target β-strands or insoluble β-fibres, either in vitro or in vivo.

Please replace the paragraph starting at page 37, line 11 of the specification with the following paragraph:

Finally, the compounds described herein may be included in a combinatorial library of such compounds to screen for one particular compound which is to be used for any of the above applications. This combinatorial library could be prepared by any suitable standard method of preparing synthetic peptide libraries (Lebl and Krchnak, 1997), wherein Nα-substituted ~~α-D-amino-acid~~ α-D-amino acid residues are included in the peptides at appropriate positions according to the present invention. The resulting library is then screened for peptides which bind to a target β-strand sufficiently tightly, or which sufficiently inhibit the activity of an oligomeric protein by blocking its oligomerisation, or which rescue cells that would otherwise be killed by the aggregation of proteins or peptides into insoluble β-fibres. The selected compounds may be used directly for any of the above applications, or used to design combinatorial

libraries of compounds which are even more active, or which are more suitable for use as therapeutic agents.

Please replace the paragraph starting at page 42, line 19 of the specification with the following paragraph:

Aggregation of the Alzheimer's Aβ peptide into amyloid fibres is caused by the intermolecular association of five-residue KLVFF (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ peptide segments comprising residues 16-20 of the Aβ peptide (Tjernberg et al., 1997). A peptide, referred to below as Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~, was therefore constructed to associate tightly with the KLVFF motif (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~, in order to inhibit aggregation of the Aβ peptide.

Please replace the paragraph starting at page 42, line 28 of the specification with the following paragraph:

The sequence of side chains in Peptide X is LLLLRR (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~, which is highly homologous to the reverse sequence FFVLK (SEQ ID NO: 3 ~~SEQ. ID. NO. 3~~), except that an additional residue having an arginine side chain has been added to the C-terminus.

Please replace the paragraph starting at page 42, line 34 of the specification with the following paragraph:

Leucine side chains were selected to take the place of all four hydrophobic side chains in the FFVLK sequence (SEQ ID NO: 3 ~~SEQ. ID. NO. 3~~) because they are relatively flexible and can adapt their conformation to make strong hydrophobic interactions with the neighbouring hydrophobic side chains of an associated β-strand, while an arginine side chain was chosen to take the place of the lysine side chain in the FFVLK sequence (SEQ ID NO: 3 ~~SEQ. ID. NO. 3~~) because it can form a stronger electrostatic interaction with one of the two acidic side chains which follow the aggregation-causing KLVFF (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ segment of the target β-strand.

Please replace the paragraph starting at page 43, line 10 of the specification with the following paragraph:

The additional residue having an arginine side chain at the C-terminus of Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ may form another strong electrostatic interaction with the second of these two acidic side chains, and should further assist Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ to penetrate cell membranes and the blood-brain barrier.

Please replace the paragraph starting at page 43, line 17 of the specification with the following paragraph:

Finally, the N-terminal amino group of Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ was acetylated to maximise its association with the aggregation-causing KLVFF segment (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ of the target β-strand, and its otherwise negatively charged C-terminal carboxyl group was amidated to further improve the ability of Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ to penetrate cell membranes and the blood-brain barrier. In this way, Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ has been designed to associate specifically as a β-strand with the aggregation-causing KLVFF (SEQ ID NO: 1) ~~(SEQ. ID. NO. 1)~~ segment of the target β-strand formed by the Alzheimer's Aβ peptide to form an parallel β-sheet complex, thereby sterically hindering the aggregation of the Aβ peptide into insoluble β-fibres.

Please replace the paragraph starting at page 43, line 31 of the specification with the following paragraph:

Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ is a substituted peptide, in accordance with the present invention. The sequence, including substituents, is Nα-acetyl-(D-leucine)-(Nα-methyl-D-leucine)-(D-leucine)-(Nα-methyl-D-leucine)-(D-arginine)-(D-arginine)-NH2, or all-D-[Ac-Leu-meLeu-Leu-meLeu-Arg-Arg-NH2.

Please replace the paragraph starting at page 44, line 1 of the specification with the following paragraph:

Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ was synthesised by 9-fluorenylmethoxycarbonyl- (Fmoc-) based solid-phase peptide synthesis (Fields and Noble, 1990) using the coupling agent 1-hydroxy-7-azabenzotriazole (HOAt), which is able to couple sterically hindered amino-acid residues (Angell et al., 1994; Carpino et al., 1994).

Please replace the paragraph starting at page 44, line 8 of the specification with the following paragraph:

Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ was found to be completely soluble in aqueous solutions over a wide range of pH values, even at a concentration of 10 mM (about 10mg/ml); yet, except for the two positively charged arginine side chains, it is extremely hydrophobic and is therefore able to penetrate cell membranes and the blood-brain barrier, especially as it is only six amino-acid residues in length. The two positively charged arginine side chains assist the peptide to penetrate cell membranes and the blood-brain barrier by making electrostatic interactions with the negatively charged phosphate head groups of their constituent phospholipid molecules, resulting in the formation of inverted micelles which carry the peptide molecules across these membranes.

Please replace the paragraph starting at page 44, line 23 of the specification with the following paragraph:

The capacity of Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ to inhibit the aggregation of a synthetic peptide fragment corresponding to residues 11 to 25 of the Alzheimer's Aβ peptide into amyloid fibrils was determined quantitatively using a standard assay based on the amyloid-dependent fluorescence of thioflavin T at 482 nm (Levine, 1993).

Please replace the paragraph starting at page 44, line 30 of the specification with the following paragraph:

Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ was dissolved in water to a concentration of 10 mM (about 10 mg/ml). Alzheimer's Aβ peptide

fragment, at a concentration of 50 μM (about 0.1 mg/ml) in 50 mM sodium acetate buffer (pH 5.0), was incubated at 25 °C in the absence or presence of Peptide X (SEQ ID NO: 2 ~~SEQ. ID. NO. 2~~) at concentrations ranging from 100 μM to 1 mM; the aggregation of the Aβ peptide fragment into insoluble β-fibres in the solutions was determined quantitatively after 20 minutes by measuring the fluorescence of 1 μM added thioflavin T at 482 nm using an excitation wavelength of 440 nm. 5ml aliquots of these solutions were then analysed by electron microscopy to confirm that Peptide X (SEQ ID NO: 2 ~~SEQ. ID. NO. 2~~) had inhibited and/or reversed the aggregation of the Alzheimer's Aβ peptide fragment into insoluble β-fibres.

Please replace the paragraph starting at page 45, line 10 of the specification with the following paragraph:

According to this assay, the aggregation of the Aβ peptide fragment into amyloid fibrils was inhibited by more than 60% in the presence of 200 μM Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ (see Fig. 5). Similar results were obtained when Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ was added to the Aβ peptide fragment after incubation, showing that Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ is able to disaggregate preformed amyloid fibrils. Analysis of the Aβ peptide fragment incubated with and without 500 mM Peptide X (SEQ ID NO: 2 ~~SEQ. ID. NO. 2~~) by electron microscopy confirmed that Peptide X (SEQ ID NO: 2 ~~SEQ. ID. NO. 2~~) had almost completely inhibited aggregation of the Aβ peptide fragment into amyloid fibrils (see Figs. 6 and 7).

Please replace the paragraph starting at page 45, line 23 of the specification with the following paragraph:

Figures 3 and 4 show how Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ forms a β-strand (X) and associates as such with one edge of a target β-strand (Y) formed by a segment of the Aβ peptide or some other peptide-based molecule in either orientation to form a parallel (Fig. 3) or antiparallel (Fig. 4) two-stranded β-sheet complex, thereby sterically hindering the association of other β-strands with that edge of the target β-strand.

Please replace the paragraph starting at page 45, line 32 of the specification with the following paragraph:

The entire length of Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ is able to form a β-strand because it consists solely of ~~α-D-amino-acid~~ α-D-amino acid residues which sterically permit it to do so: they are all able to adopt the respective phi and psi angles required to form a β-strand. Furthermore, the steric constraints imposed by the Nα-methyl groups of the two ~~Nα-methyl-α-D-amino-acid~~ Nα-methyl-α-D-amino acid residues (residues 2 and 4) serve to encourage Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ to form a β-strand. When Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ does form a β-strand, these two Nα-methyl groups lie along the same edge of the β-strand, as shown in either Figure 3 or Figure 4, because they are an even numbers of residues (in this case two residues) apart from each other and the repeating unit of a β-strand is two residues. This edge of the β-strand formed by Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~ is sterically hindered by these two Nα-methyl groups from associating with another β-strand. The other edge of the β-strand formed by Peptide X (SEQ ID NO: 2) ~~(SEQ. ID. NO. 2)~~, however, remains free to do so, and can associate in either the parallel or antiparallel orientation with a free edge of a target β-strand formed by a segment of the Aβ peptide or some other protein or peptide molecule to form a parallel (Fig. 3) or antiparallel (Fig. 4) two-stranded β-sheet complex, thereby sterically hindering the association of other β-strands with that edge of the target β-strand, and thus preventing the formation of extended β-sheets and the deposition of insoluble pathogenic β-fibres. This association of the β-strand formed by Peptide X (SEQ ID NO: 2 ~~SEQ. ID. NO. 2~~) with the target β-strand is made by hydrogen bonds between their backbone peptide groups and additional non-covalent interactions between their side chains.